REMARKS

Reconsideration and allowance are requested.

Claims 1, 3, 5-16 and 21-26 are pending.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The limitations of claims 2 and 4 are incorporated into claim 1. Support for the amendment of claim 3 may be found in paragraph [0009] on page 4 of the specification. The amendment of claims 14 and 16 is based on paragraph [0030] on page 16 of the specification (i.e., Example 3). New independent claim 22 is based on the present claim 1 and paragraph [0015] on pages 6-7 of the specification. Claims 21 and 23 are based on paragraph [0016] on page 7 of the specification. The other new claims find counterparts in the original set of claims.

35 U.S.C. 101 –Utility

Claims 1-20 were rejected because they are allegedly directed to non-statutory subject matter. Applicants traverse because the present claims clarify that the animal is not a human. This does not change the scope of the claims because it would be clear to anyone reading the Applicants' specification that their original intention was not to make the invention with humans. In fact, it is noted that referring to a human as an "animal" is ordinarily considered to be an insult because these two groups of organisms do not overlap. Thus, the ordinary meaning of "animal" does not include humans.

Withdrawal of the Section 101 rejection is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-20 were rejected under Section 112, first paragraph, because it was alleged that the specification does not reasonably provide enablement for any polymer that changes its hydration force. Applicants traverse.

As an initial matter, the Examiner did find that the specification was enabling for use of poly(N-isopropylacrylamide). Applicants submit that claim 11 is consistent with this finding of enablement. Therefore, the process of claim 11 clearly does not require undue experimentation to practice.

On page 4 of the Office Action, the Examiner alleges that the claims should be limited to using poly(N-isopropylacrylamide). But Applicants' specification teaches a variety of temperature-responsive polymers in paragraph [0016] on pages 7-8 of the specification. Polymer can be obtained by homo- or co-polymerization of monomers including (meth)acrylamide compounds, N-(or N,N-di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives. In the case of co-polymers, any two or more of these monomers may be employed. If desired, they may be co-polymerized with other monomers, or the resulting polymers may be subjected to graft polymerization or co-polymerization, or mixtures of polymers and co-polymers may be employed. Thus, it would not require undue experimentation for the skilled artisan to use temperature-responsive polymers other than poly(N-isopropylacrylamide) in accordance with the process of claim 1 (i.e., a polymer that changes its hydration force in a range of 0-80°C).

The Examiner also alleges that the specification only teaches how to use a nude mouse because other animals would reject the cancer cells. Applicants disagree. It is submitted that the claims are not limited to <u>human</u> cancer cells (see paragraph [0014] on page 6 of the specification). Although they could be transplanted into an immuno-compromised animal as stated on page 5 of the Office Action, this does not limit practice of the claimed process. An objective of the present invention is to provide a new non-human animal model free with improved functions of the cancer cells that are transplanted, and thereby avoid the problems of the prior art as described in paragraph [0004] on page 2 of the specification. Therefore, conventional techniques can be used to select a non-human animal into which cancer cells are transplanted, to treat a non-human animal that may reject the cancer cells, and to retain the transplanted cancer cells in the non-human animal. For example, the non-human animal may be treated with

an immunosuppressive drug or cancer cells may be transplanted into a syngeneic non-human animal. Thus, enablement is not limited to nude mice.

Applicants' claimed invention is characterized by detaching cultured cancer cells in the form of a sheet from its cell culture substrate using a change in the temperature, which changes hydration of thermo-sensitive polymer coated on a surface, and transplanting the sheet of cancer cells into an animal. This efficient transplantation of cancer cells was not achieved by prior art techniques. See paragraph [0007] on page 3 of the specification. The present invention has made it possible to obtain a non-human animal in which the size of a sheet of cancer tissue (i.e., tumor) in the animal can be controlled by how the sheet of cultured cancer cells is prepared.

Claims 18 and 20 are canceled. Claims 14 and 16 are clarified by reciting that the anti-tumor agent is selected on the basis that the anti-tumor agent is selected as the test substance that reduces volume and/or weight of a tumor formed from the sheet of cancer cells. Thus, claims 14 and 16 are enabled by Applicants' specification.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1-20 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Contrary to the allegation made on page 6 of the Office Action, polymers within the scope of the present claims and how changes in a polymer's hydration force can be determined in a temperature range of 0-80°C are taught by paragraphs [0015]-[0016] on pages 6-9 of the specification. From Applicants' teachings, the meanings of weak and strong hydration forces are defined in terms of the polymer's hydration and the shifts between dehydrated and hydrated states take place at 0-80°C.

The shape of transplanted cancer cells is defined in the ordinary sense of the term "sheet" which a dictionary would describe as meaning "a broad thin surface" or "an

object that is thin relative to its length and width." Thus, "sheet" does not have to be defined in the present specification.

It was alleged on page 8 of the Office Action that all cancer cell lines are transplantable. This is not correct. All cancer cell lines are not necessarily transplantable. For example, the phrase "nude mouse transplantable human cancer cell lines" (emphasis added) is found at page 785, column 1, line 22, of Koezuka et al. If all cancer cell lines were transplantable, the term "transplantable" would not have been used because its use would be redundant as it would not have modified the human cancer cell lines. In addition, the sentence "Neither transplantability in nude mice nor colony formation on soft agar was observed, except in one subline" is found in the abstract at lines 13-14 of Ichinose et al. (Jpn. J. Cancer Res., 89:516-524, 1998; enclosed). See also paragraph [0014] on pages 5-6 of the specification that teaches both types of cancer cell lines and mentions MGF-40, MGT-90, CS-C9, and CS-C20 as untransplantable cancer cell lines. Thus, it is clear that a cancer cell line may be either transplantable or untransplantable.

The phrase "the cancer cells are collected from a living tissue" means they are derived from living tissue instead of post-mortem or another cell culture before cultivation in accordance with the claimed process.

Claims 18 and 20 are canceled. Claims 14 and 16 are clarified by reciting that the anti-tumor agent is selected on the basis that the anti-tumor agent is selected as the test substance that reduces volume and/or weight of a tumor formed from the sheet of cancer cells. Thus, the meaning of claims 14 and 16 is clear when read in light of the present specification.

Other objections to the claims are overcome by deletion of the challenged limitation because it is not required for patentability, or clarification by the present amendments. Therefore, Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical

invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 4-7, 9, 12-13 and 19 were rejected under Section 102(b) as allegedly anticipated by Koezuka et al. (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994). Applicants traverse because the incorporation of the limitation from claim 2 into the independent claim shows the cited document cannot anticipate Applicants' claimed invention.

The term "intimate" is deleted from claim 5. Thus, this portion of the rejection is improper even if the claimed process was not limited to detaching cultured cancer cells in a sheet from the cell culture support because there is no evidence of placing a carrier in contact over the cultured cells at the end of cultivation in the cited document.

Moreover, the portions of this rejection directed to claims 6 and 7 fail to provide evidence that Koezuka's cancer cells are transplantable or untransplantable. The Examiner has the burden of providing evidence to support a prima facie case of anticipation so he is required to prove that the cancer cells of the cited document are a cell line and whether they can be transplanted (or not). Here, the evidence provided in the Office Action is that the cancer cells are from a primary culture (typically a mixture of different cell types) instead of a cell line resulting from multiple passaging.

Claim 9 requires collecting cancer cells from a living tissue. Koezuka disclosed that the cancer cells were directly derived from a primary culture instead of living tissue. Thus, there is no evidence provided that the cancer cells in the cited document were collected (i.e., directly derived) from living tissue.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclo-

sures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-13, 15-17 and 19 were also rejected under Section 103(a) as allegedly unpatentable over Koezuka et al. (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai et al. (JP 05-192138). Applicants traverse.

Koezuka describes a method for culturing human cancer cells by using a thermo-responsive polymer poly(N-isopropylacrylamide) and dextran sulfate. But the cultured cancer cells are detached from the cell culture substrate by treatment with trypsin. As an alternative, Koezuka discloses that when (i) a mixture of poly(N-isopropylacrylamide) and collagen was the substrate and (ii) a culture medium contained dextran sulfate, the cultured cancer cells could be detached from a primary culture on the collagen-polymer substrate only by treatment with EGTA and low temperature (at about 25°C). Here, a collagen-polymer substrate, medium containing dextran sulfate, and EGTA treatment are indispensable conditions for satisfactory detachment of cancer cells. In contrast, the present invention does not require collagen, dextran sulfate, or EGTA. A simple change in temperature results in a shift of hydration of the polymer from dehydrated to hydrated.

The Examiner alleged that Koezuka did not disclose poly(N-isopropylacrylamide). But the cited document actually does disclose the use of poly(N-isopropylacrylamide) as

the cell culture substrate when trypsin is used to detach cultured cancer cells. As stated above, the difference between the present invention and that of Koezuka is that while a collagen-polymer substrate, medium containing dextran sulfate, and EGTA treatment are indispensable for Koezuka, they are unnecessary for the present invention.

One of ordinary skill in the art would understand from Koezuka that a collagen-polymer substrate, medium containing dextran sulfate, and EGTA treatment must be used to achieve satisfactory detachment of cancer cells without trypsin. There is no evidence presented in the Office Action that the detached cancer cells are in the form of a sheet. By contrast, a cell culture substrate of poly(N-isopropylacrylamide) required trypsin for detachment according to the cited document. Koezuka's failure to teach or suggest detaching cultured cancer cells in the form of a sheet without using trypsin is not remedied by the Examiner's combination with Sakai, which discloses cultivating skin cells instead of cancer cells. Thus, the cited documents teach away from the process according to Applicants' claim 1 because the cultivation of cancer cells on a substrate of poly(N-isopropylacrylamide) required trypsin for detachment. Moreover, the combination of Koezuka and Sakai lacks a reasonable expectation of success to cultivate cancer cells on a substrate of poly(N-isopropylacrylamide) and to detach the cultivated cancer cells as a sheet by a shift in temperature. Thus, one of ordinary skill in the art would not have found it obvious to detach cultured cancer cells from a surface coated with thermo-sensitive polymer without using a proteolytic enzyme from the combination of Koezuka and Sakai.

An objective of the present invention is to provide a new non-human animal model free with improved functions of the cancer cells that are transplanted, and thereby avoid the problems of the prior art as described in paragraph [0004] on page 2 of the specification. Applicants' claimed invention is characterized by detaching cultured cancer cells in the form of a sheet from its cell culture substrate using a change in the temperature, which changes hydration of thermo-sensitive polymer coated on a surface, and transplanting the sheet of cancer cells into an animal. This efficient transplantation of cancer cells was not achieved by prior art techniques. See paragraph [0007] on page 3 of the specification. The present invention has made it possible to obtain a non-human animal in which the size of a sheet of cancer tissue (i.e., tumor) in the animal can be

controlled by how the sheet of cultured cancer cells is prepared. Thus, the combination of Koezuka and Sakai does not disclose or render obvious the present claims.

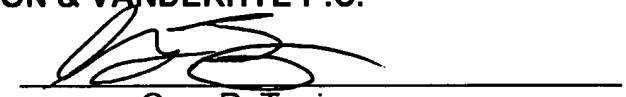
Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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1: Jpn J Cancer Res. 1998 May;89(5):516-24.

Links

Establishment and characterization of two cell lines from N-methyl-N-nitrosourea-induced mouse glandular stomach carcinomas.

Ichinose M, **Nakanishi H**, **Fujino S**, **Tatematsu M**.

Laboratory of Pathology, Aichi Cancer Center Research Institute, Nagoya.

We previously reported the induction with N-methyl-N-nitrosourea (MNU) of mouse glandular stomach carcinomas showing a gastric phenotype but variation in histologic appearance, as with human gastric carcinomas. In the present study, we established two cell lines, designated MGT-40 and MGT-93, from MNU-induced mouse glandular stomach carcinomas. These cell lines are keratin-positive and grow as epithelial monolayers in culture, requiring transforming growth factor alpha, epidermal growth factor or insulin/transferrin for optimal growth in addition to 10% fetal bovine serum. Retention of the differentiated phenotype for gastric surface mucous cells has been confirmed by cathepsin E immunohistochemistry and reverse transcriptase-polymerase chain reaction for mouse spasmolytic polypeptide. Neither transplantability in nude mice nor colony formation on soft agar was observed, except in one subline. Chromosome analysis revealed aneuploidy with modal chromosome numbers ranging from 58 to 78 and no specific structural abnormalities. This is the first report of cell lines derived from mouse glandular stomach carcinomas. They should prove useful for studies of the mechanisms of regulation of growth and differentiation.

PMID: 9685855 [PubMed - indexed for MEDLINE]

Related articles

Induction of adenocarcinomas in the glandular stomach of BALB/c mice treated with N-methyl-N-nitrosourea. [Jpn J Cancer Res. 1992]

N-methyl-N-nitrosourea concentration-dependent, rather than dose-dependent, induction of adenocarcinomas in the glandular stomach of BALB/c mice. [Jpn J Cancer Res. 1998]

Clonal analysis of glandular stomach carcinogenesis in C3H/HeN ↔ BALB/c chimeric mice treated with N-methyl-N-nitrosourea. [Cancer Res. 1994]

Review [Eradication model employing Mongolian gerbils treated with chemicals and infected with Helicobacter pylori--implications for human cancer prevention] [Nippon Rinsho. 2000]

Review Tumours of the glandular stomach. [IARC Sci Publ. 1996]

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